Remarks

Priority

As correctly noted by the Examiner, the pending application was filed on January 22, 2002. Claims 1 and 16 as originally filed in the pending application specified that the microparticles have "a total surface area greater than about 0.5 m^2/mL". This limitation was also disclosed in parent application, U.S.S.N. 09/433,486, filed November 4, 1999 (now U.S. Patent No. 6,395,300) in claims 1 and 23 as originally filed. Therefore, claim 16 as pending is supported by the specification as originally filed and is entitled to its priority claim to U.S.S.N. 09/433,486, filed November 4, 1999.

Rejection Under 35 U.S.C. § 103

Claims 16-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2001/0018072 to Unger ("Unger"), U.S. Patent No. 6,565,885 to Tarara *et al.* ("Tarara"), U.S. Patent No. 5,21,961 to Mathiowitz *et al.*, ("Mathiowitz"), or U.S. Patent No. 5,413,797 to Khan *et al.* ("Khan"). Applicants respectfully traverse this rejection.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

a. The claimed method

Independent claim 16 and its dependent claims, claims 17-21, define methods for making a pharmaceutical composition that contains a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug. As specified in claim 16, the method requires the following steps:

(a) dissolving a drug in a volatile solvent to form a drug solution,

(b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution.

(c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and

(d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient.

Independent claim 16 also specifies a number of features that must be present in the resulting composition. The composition contains microparticles of drug that have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 m^2/mL. Additionally the composition contains a dry porous matrix in a dry powder form, which has a TAP density less than or equal to 1.0 g/mL and a total surface area of greater than or equal to 0.2 m^2/g. As discussed in detail below none of the references cited by the Examiner make obvious the claimed method.

b. U.S. Patent Application Publication No. 2001/0018072 to Unger ("Unger")

Unger describes a solid porous matrix containing a surfactant and a bioactive agent. In one embodiment, the matrix is formed by spray drying a solvent, surfactant, therapeutic agent, and blowing agent (para. 0076). The therapeutic agent is suspended in the solvent since it is "only marginally soluble in the solvent." (para. 0075). In contrast, independent claim 16 specifies that the drug is dissolved in the solvent. A therapeutic agent which is only marginally soluble in the solvent, will not dissolve to form a drug solution, as required by claim 16. Further, the only blowing agent disclosed by Unger is a liquid blowing agent, methylene chloride, which is not a volatile solid (*see* para. 0022).

Unger explains that a gaseous precursor "may be useful as a solvent in the preparation of the solid porous matrix [...and] may be added to the surfactant and therapeutic and removed during processing." (para. 0161) Unger defines the solvent as "a suspending medium for associating the surfactant with the therapeutic" (para. 0075), and states that preferred solvents are

"gaseous precursors" (para. 0074). Thus, in this embodiment, the gaseous precursor is the solvent. Clearly, for this to occur, the gaseous precursor cannot be in the form of a volatile solid, as required by claim 16.

In another embodiment, Unger notes that a gaseous precursor may be incorporated in the microparticles, where the gaseous precursor is a material that is "capable of being converted to a gas in vivo." (para. 0164). Thus, suitable precursors for this embodiment, may be in the liquid or solid form. However, these precursors are not removed by spray drying, as required by claim 16.

Thus, Unger does not disclose or suggest combining a volatile solid pore-forming agent with the drug solution, and then removing the volatile solvent and the pore forming agent to form a porous matrix of drug and excipient, as required by claim 16.

Further, as noted above, claim 16 specifies the properties of the compositions formed using the claimed method. Unger does not disclose or suggest that the microparticles formed using its process have these properties. Further, one of ordinary skill in the art would not be motivated to modify Unger to arrive at the claimed methods. Therefore claims 16-21 are not obvious in view of Unger.

c. U.S. Patent No. 6,565,885 to Tarara et al. ("Tarara")

The Examiner repeated the previous rejection of claims 16-21 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,565,885 to Tarara *et al.* ("Tarara"), and stated that this rejection "is maintained pending receipt of legible copy of the Exhibit A". (Office Action at

page 7). In response, applicants resubmit the Declaration under 37 C.F.R. § 1.131 by Julie Straub and Howard Bernstein, along with the Exhibits referenced therein.

Applicants presented extensive arguments in response to this rejection in the Response to Office Action filed March 8, 2006, and have copied them below for the Examiner's convenience.

Tarara issued as a patent on May 20, 2003. Tarara's earliest claimed priority date is to provisional application, U.S.S.N. 60/060,337, filed September 29, 1997. The present application was filed on January 22, 2002 and claims priority to an application filed on May 27, 1999. Thus, Tarara was clearly published after the priority date of the present application, and could only be prior art under 35 U.S.C. §102(e). Assuming that the Examiner rejected the claims for obviousness based on a determination that Tarara is prior art under 35 U.S.C. §102(e), this rejection is respectfully traversed.

Legal Standard under 35 U.S.C. § 102(e)

35 U.S.C. §102(e) prior art includes patents "granted on an application for patent by another filed in the United States *before the invention by the applicant* for patent" 35 U.S.C. §102 (e) (emphasis added). A declaration under 37 C.F.R. § 1.131 may be used to "establish invention of the subject matter of the rejected claims prior to the effective date of the reference [...] on which the rejection is based." 37 C.F.R. § 1.131 (a). The declaration must show either (1) reduction to practice of the invention prior to the effective date of the reference or (2) conception of the invention prior to the effective date, coupled with due diligence from the effective date until a subsequent reduction to practice or the filing of the application. Chisum on

Patents §3.08[1]. When a reference shows only part of the invention, such as a species within a generic invention, a Rule 131 affidavit is sufficient if it shows that the affiant had prior possession of that part of the invention disclosed by the reference. Chisum on Patents §3.08[1][b]. *In re Stempel*, 241 F.2d 755, 113 U.S.P.Q. 77 (C.C.P.A. 1957), the leading case on prior possession of part of an invention, explained that a reference "is valid only for what it discloses [therefore] if the application establishes priority with respect to that disclosure, and there is no statutory bar [the reference] is of no effect at all." 241 F.2d at 759-60. Therefore, a declaration under 37 C.F.R. § 1.131 is only required to antedate what is disclosed by the reference.

Tarara Is Not Available as Prior Art Under 35 U.S.C. § 102(e)

Tarara claims priority to a provisional application filed on September 29, 1997. Tarara discloses using a spray drying feedstock which contains a bioactive agent, surfactant, and a blowing agent, optionally with an excipient (abstract; col. 17, lines 11-16). Some of Tarara's preferred embodiments also contain synthetic or natural polymers (see col. 11, line 63 to col. 12, line 16).

Enclosed is a declaration under 37 C.F.R. § 1.131 by Julie Straub and Howard Bernstein. In their declaration, Julie Straub and Howard Bernstein state that prior to September 29, 1997, the earliest claimed priority date for Tarara, they conceived of and reduced to practice compositions that are formed by spray drying a feedstock containing a bioactive agent, a surfactant and a blowing agent. A declaration containing the same statements and data as the

statements and data in the enclosed declaration was previously filed in related application, U.S.S.N. 09/706,045, which issued as U.S. Patent No. 6,932,983 on August 23, 2005, to overcome a similar rejection over Tarara.

As noted in the copies of the laboratory notebook pages attached to the Declaration (Exhibit A), microparticles containing air as the diagnostic agent were formed by spray drying (see page 14). Air bubbles were encapsulated in synthetic polymer microparticles by a spray drying process. The feed stock to the spray drying apparatus included a blowing agent (ammonium acetate), a surfactant (lecithin), polymers (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25) and D,L-poly(lactide)), and a diagnostic agent (air). This composition was homogenized to form an emulsion, which was then spray dried using a small-scale lab spray dryer. The resulting microparticles were echogenic (see page 105, injection 7).

Tarara defines "blowing agent" as "any volatile substance, which can be incorporated into the feed solution for the purpose of producing a perforated foam-like structure in the resulting dry microspheres." (col. 19, lines 26-29). Tarara specifically lists "[d]issolved or dispersed salts or organic substances which can be removed under reduced pressure by sublimation in a post-production step, such as ammonium salts, camphor, etc." (col. 19, lines 52-55). Thus ammonium acetate is a representative species of the genus of blowing agents disclosed in Tarara.

Tarara defines "bioactive agent" as "a substance which is used in connection with an application that is therapeutic or diagnostic in nature." (col. 6, lines 30-32). Tarara explains that

"those skilled in the art will appreciate that any therapeutic or diagnostic agent may be incorporated in the stabilized dispersions." (col. 6, lines 35-37) Air is a gas used in echogenic particles for ultrasound imaging techniques (*see e.g.* Appendix A, page 105, injection 7). Thus, air is a representative species of the genus of bioactive agents disclosed in Tarara.

Tarara defines "surfactants" as "any compound or composition that aids in the formation of perforated microparticles or provides enhanced suspension stability, improved powder dispersibility or decreased particle aggregation." (col. 10, lines 14-18) Tarara specifically mentions lecithin as a typical surfactant (*see* col. 31, line 57). Thus, lecithin is a representative species of the genus of surfactants disclosed in Tarara.

As shown by the attached declaration and copies of pages from the inventor's laboratory notebook, prior to September 29, 1997, applicants had conceived of and reduced to practice forming particles by spray drying a feedstock which contains a bioactive agent, surfactant, and blowing agent. Therefore, Tarara is not available as prior art under 35 U.S.C. § 102(e), and claims 16-21 are not obvious in view of Tarara.

Tarara's earliest priority date for the relevant disclosure is September 29, 1998

The Examiner's attention is directed to the fact that the earliest disclosure of including a volatile salt in the feed stock to the spray dryer is September 28, 1998, the filing date of PCT/US98/20602. The first three applications to which Tarara claims priority, do not disclose using volatile salts as the blowing or inflating agent. WO 99/16419, filed as PCT/US98/20602 on September 29, 1998, is the first priority application that lists a volatile salt as a suitable

blowing agent. At page 17, lines 8-9 and page 20, lines 29-30, WO 99/16419 states that ammonium carbonate and camphor are suitable blowing agents. Therefore, Tarara's earliest priority date for the disclosure of including a volatile salt in the spray dried composition, as required by the pending claims, should be September 29, 1998. However, regardless of the priority date accorded Tarara, the enclosed declaration establishes that the applicants conceived of and reduced to practice compositions that are formed by spray drying a diagnostic agent with a surfactant and a blowing agent prior to the earliest priority date of Tarara.

d. U.S. Patent No. 5,413,797 to Khan et al. ("Khan")

Khan discloses compositions for the controlled release of adrenocorticotropic hormone (ACTH) and methods of making the ACTH compositions (abstract). The preferred process for forming the compositions, i.e. a rapid freezing solvent extraction process, requires the following steps: (1) dissolving a polymer in a solvent together with powdered ACTH; (2) atomizing the solution/suspension into a vessel containing a frozen non-solvent, which is overlayed with a liquefied gas, at a temperature below the freezing point of the polymer/active agent solution/suspension, to form frozen microspheres; (3) allowing the frozen microspheres to sink onto the frozen non-solvent layer; (4) allowing the frozen non-solvent to thaw and the frozen microspheres to sink into the liquid non-solvent; (5) allowing the solvent in the microspheres to thaw; and (6)slowly extracting the solvent into the non-solvent, resulting in hardened microspheres containing ACTH. (*see* col. 2, lines 28- 48). In contrast, claim 16 contains a number of different process steps, such as (1) combining at least one volatile solid pore forming

agent with a drug solution to form an emulsion, suspension, or second solution; and (2) removing a volatile solvent and the pore forming agent from the emulsion, suspension, or second solution to yield a porous matrix of drug and excipient.

Khan explains that other processes for forming microparticles have disadvantages. For example, when describing the spray drying method, Khan states "[s]pray drying is not preferred since it may result in some loss of activity due to the heat generated in the process as well as in loss of considerable amounts of the material due to sticking of the polymer to the large surface area on the sides of the chamber." (col. 3, lines 64-68). With respect to the solvent evaporation method, Khan states that this method is "not preferred since the amount of incorporated material is usually lower than the theoretical values due to loss of drug to the aqueous phase." (col. 4, lines 24-27). With respect to the phase separation method, Khan states that when this method is used "active agent is lost during the solvent extraction process [...and] biologically active proteins may be denatured." (col. 4, lines 51-55).

As noted above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The Examiner acknowledges that "Khan does not disclose the exact process steps [defined by the pending claims]." (Office Action, at page 7) Further, Khan does not suggest the claimed method nor provide one of

ordinary skill in the art with the motivation to modify its method to correspond with the claimed method. For example, Khan does not disclose or suggested combining at least one volatile solid pore forming agent with a drug solution to form an emulsion, suspension, or second solution, as required by claim 16. Further, Khan does not disclose or suggest removing a volatile solvent and the pore forming agent from the emulsion, suspension, or second solution to yield a porous matrix of drug and excipient, as required by claim 16. Finally, Khan points out a number of disadvantages inherent in spray drying and solvent evaporation processes, which are included in the list of suitable processes for step (d), as defined by claim 17. Therefore, claims 16-21 are non-obvious in view of Khan.

e. U.S. Patent No. 5,271,961 to Mathiowitz et al. "(Mathiowitz")

Mathiowitz discloses a method for forming protein microspheres. The method requires: (1) dissolving the protein in a first solvent which is a water-miscible organic, organic/aqueous, or binary organic solvent, acid, base or salt solution (the encapsulating phase); (2) adding the compound to be incorporated, in the form of a suspension, emulsion, solution or particles, to the protein solution; (3) adding a second liquid phase (the continuous phase) to the protein-containing mixture, where the second liquid phase does not dissolve the proteins and has limited miscibility with the first solvent; (4) applying vigorous agitation; and (5) removing the first solvent under conditions sufficient to form microspheres, such as by evaporation or extraction. (col. 3, lines 30-43). In contrast, claim 16 contains a number of different process steps, such as (1) combining at least one volatile solid pore forming agent with a drug solution to form an

emulsion, suspension, or second solution; and (2) removing a volatile solvent and the pore forming agent from the emulsion, suspension, or second solution to yield a porous matrix of drug and excipient.

As discussed above with respect to Khan, Mathiowitz does not meet the criteria for establishing a *prima facie* case of obviousness. The Examiner acknowledges that "Mathiowitz does not disclose the exact process steps [defined by the pending claims]." (Office Action, at page 7). Further, Mathiowitz does not suggest the claimed method nor provide one of ordinary skill in the art with the motivation to modify its method to correspond with the claimed method. For example, Mathiowitz does not disclose or suggest combining at least one volatile solid pore forming agent with a drug solution to form an emulsion, suspension, or second solution, as required by claim 16. Further, Mathiowiz does not disclose or suggest removing a volatile solvent and the pore forming agent from the emulsion, suspension, or second solution to yield a porous matrix of drug and excipient, as required by claim 16. Therefore, claims 16-21 are non-obvious in view of Mathiowitz.

Double Patenting Rejection

Claims 16-21 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 11-14 of U.S. Patent No. 6,932,983 to Straub *et al*. Applicants will submit a terminal disclaimer once the claims are otherwise determined to be patentable.

New Claim

New claim 34, which depends from claim 16 and further defines the drug, has been added. Support for new claim 34 can be found in the specification at least at page 7, lines 9-17; page 7, line 31 until page 8, line 4; page 8, lines 15-16; page 9, lines 1-4 and 10-14; and page 9, line 22 until page 10, line 12.

Allowance of claims 16-21 and 34 is respectfully solicited.

Respectfully submitted,

/Rivka D. Monheit/
Rivka D. Monheit
Reg. No. 48,731

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PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2152
(404) 879-2160 (Facsimile)